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Longitudinal analyses of serum metabolite phenotypes in the EarlyBird cohort identify metabolic readouts associated with childhood insulin resistance

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Background and aims: Metabolite signatures have emerged as biomarkers associated with insulin resistance (IR) and type 2 diabetes (T2D). These biomarkers have potential to elucidate the mechanisms linking obesity to IR, and identify individuals at risk of T2D, but there are few longitudinal data in children through adolescence, when IR undergoes profound changes. Longitudinal studies in healthy children are essential to resolve whether altered metabolite signatures precede the development of IR. We conducted longitudinal modelling of metabonomic and clinical data from the Earlybird cohort to determine whether metabolite signatures are associated with IR.

Materials and methods: EarlyBird is a non-intervention prospective cohort study (347 healthy UK children followed throughout childhood and puberty). Annual fasting serum samples from a sub-group of 150 children underwent metabonomic profiling by proton nuclear magnetic resonance spectroscopy. Subjects were chosen to represent the range of blood glucose observed in the cohort from 5y to 16y. We applied a combination of methods: consensus based clustering (CClust), and mixed effects modelling (MEM). CClust was used to group children according to their temporal profile of IR (HOMA-IR). Non-parametric testing was performed at each time point, and results aggregated according to the Fisher method to identify influential variables. MEM was used to assess the association between HOMA-IR and individual metabolites, taking into account age, BMI, physical activity and pubertal timing.

Results: MEM identified several metabolites that were significantly and inversely associated ($p < 0.05$) with IR across childhood independently of BMI sds, physical activity and age at peak height velocity. Amongst the most influential metabolites were ketone bodies, branched amino acids, histidine, glutamine, lysine, and creatine. CClust analyses of HOMA-IR trajectories were performed at pre-puberty and

adolescence, for both genders (f, females, m, males). This enabled the identification of metabolic patterns of high IR status at specific biological ages. At puberty IR was associated with reduced concentrations of amino acids histidine (f adj. $p=0.09$, m adj. $p=0.02$), glutamine (f adj. $p=0.09$, m adj. $p=0.03$), lysine (f adj. $p=0.09$, m adj. $p=0.007$) and valine (f adj. $p=0.09$, m adj. $p=0.02$). Additional patterns in central energy metabolism at puberty were increased 3D-hydroxybutyrate (f adj. $p=0.09$, m adj. $p=0.003$) and reduced creatine (f adj. $p=0.08$, m adj. $p=0.007$).

Conclusion: The integrative approach developed here enabled us to explore the interactions between metabolite signatures and IR over time, during pubertal development. Several metabolites were associated with IR in children independently of pubertal development, adiposity and physical activity. This longitudinal analysis in healthy children confirms that IR is associated with complex but changing metabolite signatures. Amino acid signatures observed in more obese populations may be consequences rather than antecedents of IR. Ketogenesis was inversely associated with IR throughout childhood, but became positively associated with IR in puberty. Longer term observational studies may show whether these metabolite signatures predict adult health risks such as T2D, or could be used as a basis for intervention.